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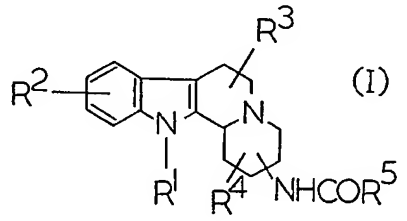
(54) INDOLOQUINOLIZINES

(71) We, JOHN WYETH & BROTHER LIMITED, of Huntercombe Lane South, Taplow, Maidenhead, Berkshire, a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new indole derivatives to processes for the preparation thereof, and to pharmaceutical compositions containing such derivatives.

More particularly the present invention provides compounds having the general formula



(I)

wherein R^1 represents hydrogen, lower alkyl, lower aralkyl or aroyl; R^2 represents hydrogen, halogen, lower alkoxy, hydroxy or lower alkyl; R^3 represents hydrogen, hydroxy, lower alkyl or an oxo group; R^4 represents hydrogen halogen or lower alkyl; and R^5 represents aryl (including heteroaryl) lower alkoxy, aryloxy, lower aralkyloxy, lower aralkyl, diaryl lower alkyl, or a cycloalkyl radical containing from 5 to 7 carbon atoms; and the acid addition and quaternary ammonium salts thereof.

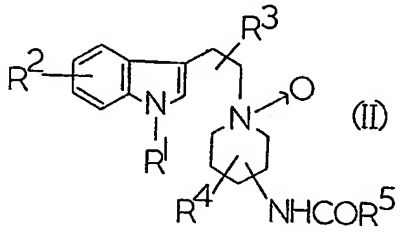
The terms "lower alkyl" and "lower alkoxy" as used herein indicate that the alkyl and alkoxy radicals each contain from 1 to 6 carbon atoms. Those radicals containing 1 to 4 carbon atoms are preferred. The terms "lower aralkyl" and "lower aralkyloxy" indicate that the aralkyl and aralkyloxy radicals each contain from 7 to 10, preferably 7 to 9, carbon atoms.

Examples of the group R^1 are hydrogen, methyl, ethyl, n - propyl, isopropyl, n - butyl, isobutyl, benzyl, benzoyl and p - chloro - benzyl. Preferably R^1 is hydrogen or methyl. Examples of R^2 are hydrogen, chlorine, methoxy, ethoxy, hydroxy, methyl, ethyl, n - propyl, isopropyl, n - butyl or isobutyl. Preferably R^2 is a hydrogen atom. Examples of the group R^3 are hydrogen, hydroxy, oxo, methyl, ethyl, n - propyl, isopropyl and n - butyl. Preferably R^3 is hydrogen or methyl. The group R^4 can be, for example, hydrogen, chlorine, methyl, ethyl, n - propyl, isopropyl, n - butyl or isobutyl. Preferably R^4 is a hydrogen atom. Examples of R^5 are phenyl, substituted phenyl (for example phenyl substituted by halogen, such as chlorine; by alkoxy, such as methoxy or ethoxy; by alkyl, such as methyl or ethyl; by trifluoromethyl; or by methylenedioxy), heteroaryl (such as 3 - indolyl, 2 - thienyl or 2 - furyl), methoxy, ethoxy, phenoxy, benzyl, benzyloxy, diphenylmethyl or cyclohexyl.

Examples of the acid addition salts are the hydrochloride, hydrobromide, hydroiodide, sulphate, phosphate, citrate, maleate, tartrate, succinate and fumarate. Examples of the quaternary ammonium salts are those formed by addition of methyl bromide or methyl iodide.

The novel compounds provided by the present invention possess pharmacological properties and/or may be intermediates for the other compounds of this invention. In particular the novel compounds of this invention generally possess hypotensive activity.

The novel compounds of general formula (I) may be prepared by a number of processes. A first general method of preparation comprises cyclising a compound of general formula:

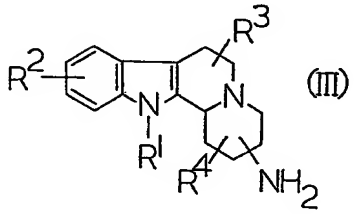


(II)

wherein R^1, R^2, R^3, R^4 and R^5 are as hereinbefore defined. The cyclisation of compounds of general formula (II) may be brought about in a number of ways. For example a compound of formula (II) may be cyclised by heating in the presence of ferrous ions and a suitable acidic medium. Examples of suitable acidic media are methanol/acetic acid or sulphuric acid/pyridine. Examples of compounds giving ferrous ions are ferrous sulphate or ferrous chloride. Methods for preparing the N - oxides of formula II and the compounds themselves, used as starting materials for the above reaction, are disclosed in our co-pending Patent Application No. 25298/73 (Serial No. 1,435,572).

Alternatively cyclisation of compounds of general formula (II) to give compounds of general formula (I) may be accomplished by reaction with trifluoroacetic anhydride/H^+ mixtures, e.g. a mixture of trifluoroacetic anhydride and trifluoroacetic acid.

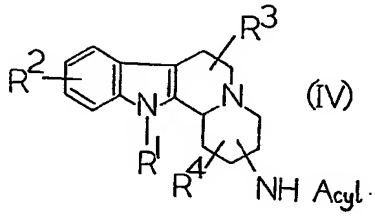
A further process for preparing the novel compounds of this invention comprises reacting a compound of general formula



(III)

wherein R^1, R^2, R^3 and R^4 are as defined above, with (i) a reactive derivative of an acid of general formula R^5COOH, wherein R^5 represents aryl (including heteroaryl), lower aralkyl, diaryl lower alkyl or a cycloalkyl radical; or (ii) a haloester of general formula $XCOR^5$ wherein X represents a halogen atom and R^5 represents lower alkoxy, aryloxy and lower aralkyloxy. As a reactive derivative of the acid of formula R^5COOH used in the process described above, it is preferably usually to use a halide (for example the chloride or bromide) or an anhydride. Other examples of reactive derivatives of the acid R^5COOH which may be used are the acid azide, mixed anhydrides and active esters. Furthermore the compounds of formula (I) wherein R^5 is as defined in connection with formula R^5COOH may also be prepared by treating a compound of formula (III) with the acid R^5COOH in the presence of a known condensing agent (for example, a carbodiimide), or by first activating the amino function (for example, by forming the phosphazo derivative and then reacting with the acid R^5COOH. In connection with the introduction of the $—COR^5$ group into a compound of formula (III); reference may be made to "Chemistry of the Amino Acids" by Greenstein and Winitz (John Wiley & Sons. Inc., Publishers, 1961) at pages 782—883 and 943—1108.

The compound of formula III, used as starting material in the process above, may be prepared by hydrolysing a corresponding acylamino compound of general formula:



(IV)

wherein R^1, R^2, R^3 and R^4 are as defined above and "Acyl" represents an acyl radical e.g. acetyl or benzoyl. The hydrolysis may be carried out using a mineral acid, such as hydrochloric acid.

When a compound of general formula (I) is prepared in which R^1 is hydrogen then that compound may be lower alkylated, lower aralkylated or aroylated at the 12-position by methods known *per se* to give the other compounds of formula (I) in which R^1 represents lower alkyl, lower aralkyl, or aroyl. For example an alkali metal salt, e.g. the sodium salt may be prepared and reacted with a lower alkyl- or a lower aralkyl - halide or with an aroylating agent.

A further aspect of the invention is the provision of a pharmaceutical composition comprising a compound of general formula I, or a pharmaceutically acceptable acid addition or quaternary ammonium salt thereof, together with a pharmaceutical carrier. Any suitable carrier known in the art may be used to prepare the pharmaceutical compositions. In such a composition the carrier may be solid, liquid or a mixture of solid and liquid. In the solid form the compositions include powders, tablets and capsules. In the liquid or solid liquid form the compositions include solutions, suspensions and creams.

Preferably the pharmaceutical composition is in unit dosage form. In such form, the composition is sub-divided in unit doses containing appropriate quantities of the active ingredient; the unit dosage form can be a

packaged composition, the package containing specific quantities of compositions, for example packeted powders or vials or ampoules. The unit dosage form can be a capsule, cachet or tablet itself, or it can be the appropriate number of any of these in packaged form. The quantity of active ingredient in a unit dose of composition may be varied or adjusted from 5 mg or less to 500 or more, according to the particular need and the activity of the active ingredient. The invention also includes the compounds in the absence of carrier where the compounds are in unit dosage form.

When the compounds of this invention are employed as hypotensive agents they may be administered to warm blooded animals, e.g. mice, rats, rabbits, dogs, cats or monkeys alone or in combination with pharmaceutically acceptable carriers, the proportion of which is determined by the solubility and chemical nature of the compounds, chosen route of administration and standard biological practice. For example, they may be administered orally in the form containing such excipients for example starch, milk or sugar, e.g. as tablets or capsules. They may also be administered orally in the form of solutions or they may be injected as solutions. For intraperitoneal administration they may be used in the form of sterile solutions or suspensions containing other solutes for example enough saline or glucose to make the solution isotonic.

The dosage of the present compounds will vary with the mode of administration and the particular compound chosen. Furthermore, it will vary with the particular subject under treatment. Generally, treatment is initiated with doses substantially less than the optimum dose of the compound. Thereafter, the dosage may be increased by small amounts until the optimum effect under the circumstances is reached. In general, the compounds of this invention are most desirably administered at a concentration level that will generally afford effective results without causing any harmful or deleterious side effects.

The following non-limiting examples illustrate the invention:

EXAMPLE 1

1,2,3,4,6,7,12,12b - Octahydro - 2 - benzamido - indolo[2,3 - a] - quinolizine

4 - Benzamido - 1 - [2 - (indol - 3 - yl)ethyl]piperidine - N - oxide (36.4 g, 0.10 mole) was suspended in methanol (4 litres) and ferrous sulphate heptahydrate (100 g), followed by glacial acetic acid (750 mls), were added. The mixture was refluxed for 18 hours, allowed to cool, and H_2S bubbled through for 10 minutes. Sodium borohydride (300 g) was added portionwise, with stirring and cooling, and H_2S was passed through for a further 30 minutes. After standing for 1 hour, the mixture was filtered (Kieselguhr); the filtrate was evaporated to dryness; then water (250 mls) and 10N sodium hydroxide solution added until strongly basic. The alkaline solution was extracted thoroughly with benzene, and then the benzene was washed with water before drying ($MgSO_4$). Evaporation afforded a mixture of the title compound and de-oxygenated starting material (7.70 g). Chromatography, using a basic alumina column and gradient elution with benzene/ethyl acetate gave the pure title compound (1.16 g). Recrystallation from methanol/ether/HCl provided the hydrochloride hydrate as colourless needles, m.p. 276°.

Found: C, 68.44; H, 6.49; N, 10.61%
$C_{22}H_{23}N_3O$. HCl . 1/4 . H_2O requires:
C, 68.38; H, 6.39; N, 10.87%.

EXAMPLES 2 to 23

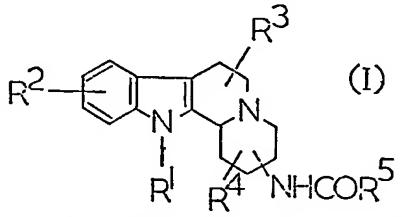
By procedures analogous to Example 1 the following compounds can be prepared:

2. 1,2,3,4,6,7,12,12b - Octahydro - 2 - [4 - chlorobenzamido]indolo[2,3 - a] - quinolizine.
3. 1,2,3,4,6,7,12,12b - Octahydro - 2 - [3 - chlorobenzamido]indolo[2,3 - a] - quinolizine.
4. 1,2,3,4,6,7,12,12b - Octahydro - 2 - [4 - methoxybenzamido]indolo[2,3 - a]quinolizine.
5. 1,2,3,4,6,7,12,12b - Octahydro - 2 - [3 - methoxybenzamido]indolo[2,3 - a]-quinolizine.
6. 1,2,3,4,6,7,12,12b - Octahydro - 2 - [2 - methoxybenzamido]indolo[2,3 - a] - quinolizine.
7. 1,2,3,4,6,7,12,12b - Octahydro - 2 - [4 - methylbenzamido]indolo[2,3 - a] - quinolizine.
8. 1,2,3,4,6,7,12,12b - Octahydro - 2 - [3 - methylbenzamido]indolo[2,3 - a] - quinolizine.
9. 1,2,3,4,6,7,12,12b - Octahydro - 2 - [2 - methylbenzamido]indolo[2,3 - a] - quinolizine.
10. 1,2,3,4,6,7,12,12b - Octahydro - 2 - phenylacetamido - indolo[2,3 - a] - quinolizine.
11. 1,2,3,4,6,7,12,12b - Octahydro - 2 - benzamido - 12 - methyl - indolo[2,3 - a]quinolizine.
12. 1,2,3,4,6,7,12,12b - Octahydro - 2 - [4 - chlorobenzamido] - 12 - methyl-indolo[2,3 - a]quinolizine.
13. 1,2,3,4,6,7,12,12b - Octahydro - 2 - [4 - methylbenzamido] - 12 - methyl - indolo[2,3 - a]quinolizine.
14. 1,2,3,4,6,7,12,12b - Octahydro - 2 - [4 - methoxybenzamido] - 12 - methyl-indolo[2,3 - a]quinolizine.

15. 1,2,3,4,6,7,12,12b - Octahydro - 2 - benzamido - 12 - benzyl - indolo[2,3 - a]quinolizine.
16. 1,2,3,4,6,7,12,12b - Octahydro - 2 - cyclohexanecarboxamido - indolo - [2,3 - a]quinolizine.
17. 1,2,3,4,6,7,12,12b - Octahydro - 2 - cyclopentanecarboxamido - indolo - [2,3 - a]quinolizine.
18. 1,2,3,4,6,7,12,12b - Octahydro - 2 - cycloheptanecarboxamidoindolo[2,3 - a]-quinolizine.
19. 1,2,3,4,6,7,12,12b - Octahydro - 2 - benzamido - 7 - hydroxy - indolo - [2,3 - a]quinolizine.
20. 1,2,3,4,6,7,12,12b - Octahydro - 2 - [4 - methoxybenzamido] - 7 - hydroxy-indolo[2,3 - a]quinolizine.
21. 1,2,3,4,6,7,12,12b - Octahydro - 2 - benzamido - 10 - methoxy - indolo - [2,3 - a]quinolizine.
22. 1,2,3,4,6,7,12,12b - Octahydro - 2 - [4 - chlorobenzamido] - 10 - methoxy-indolo[2,3 - a]quinolizine.
23. 1,2,3,4,6,7,12,12b - Octahydro - 2 - benzamido - 7 - oxo - indolo - [2,3 - a]-quinolizine.

WHAT WE CLAIM IS:—

1. A compound having the general formula:



(I)

wherein R^1 represents hydrogen, lower alkyl, lower aralkyl or aroyl; R^2 represents hydrogen, halogen, lower alkoxy, hydroxy or lower alkyl; R^3 represents hydrogen, hydroxy, lower alkyl or an oxo group; R^4 represents hydrogen, halogen or lower alkyl; and R^5 represents aryl (including heteroaryl) lower alkoxy, aryloxy, lower aralkyloxy, lower aralkyl, diaryl lower alkyl, or a cycloalkyl radical containing from 5 to 7 carbon atoms; and the acid addition and quaternary ammonium salts thereof.

2. A compound as claimed in Claim 1 wherein R^1 is hydrogen or methyl.

3. A compound as claimed in Claim 1 wherein R^1 is benzyl or benzoyl.

4. A compound as claimed in any one of Claims 1 to 3 wherein R^2 represents hydrogen, chlorine, methoxy or methyl.

5. A compound as claimed in any one of Claims 1 to 4 wherein R^3 represents hydrogen, hydroxy or methyl.

6. A compound as claimed in any one of Claims 1 to 5 wherein R^4 represents hydrogen or methyl.

7. A compound as claimed in any one of Claims 1 to 6 wherein R^5 is substituted or unsubstituted phenyl, indolyl, thienyl, furyl, benzyl or cyclohexyl.

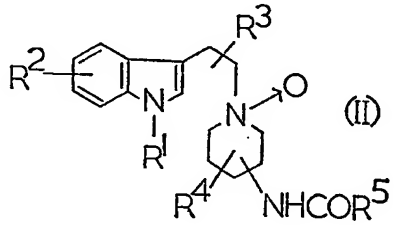
8. A compound as claimed in Claim 7 wherein R^5 is phenyl or phenyl substituted by chlorine, methoxy, ethoxy, trifluoromethyl, methyl, ethyl or methylenedioxy.

9. 1,2,3,4,6,7,12,12b - Octahydro - 2 - benzamido - indolo[2,3 - a]quinolizine.

10. A compound as claimed in any one of Claims 1 to 9 when in the form of an acid addition or quaternary ammonium salt.

11. A compound as claimed in Claim 10 wherein the acid addition salt is the hydrochloride, hydrobromide, sulphate, maleate, tartrate, succinate or fumarate.

12. A process for preparing a compound as claimed in Claim 1 which comprises cyclising a compound of general formula:



(II)

wherein R^1, R^2, R^3, R^4 and R^5 are as defined in Claim 1.

13. A process as claimed in Claim 12 wherein the cyclisation is carried out by heating in the presence of ferrous ions and a suitable acidic medium.

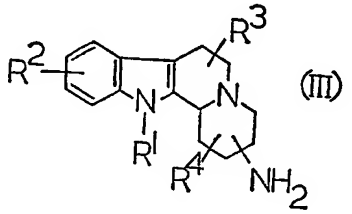
14. A process as claimed in Claim 12 wherein the acidic medium is methanol/acetic acid or sulphuric acid/pyridine.

15. A process as claimed in Claim 13 or Claim 14 wherein the ferrous ions are provided by ferrous sulphate or ferrous chloride.

16. A process as claimed in Claim 12 wherein the cyclisation is accomplished by reaction with trifluoroacetic anhydride/$H^{\oplus}$ mixtures.

17. A process as claimed in Claim 16 wherein the $H^{\oplus}$ in the trifluoroacetic anhydride/$H^{\oplus}$ mixture is provided by trifluoroacetic acid.

18. A process for preparing a compound of formula I which comprises reacting a compound of general formula:



(III)

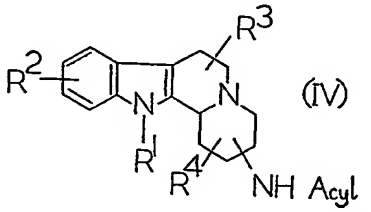
wherein R^1, R^2, R^3 and R^4 are as defined in Claim 1 (i) with a reactive derivative of an acid of general formula R^5COOH, or with a condensing agent and an acid of general formula R^5COOH wherein R^5 represents aryl (including heteroaryl), lower aralkyl, diaryl lower alkyl or a cycloalkyl radical; or (ii) with a haloester of general formula $XCOR^5$ wherein X represents a halogen atom and R^5 represent lower alkoxy, aryloxy and lower aralkyloxy.

19. A process as claimed in Claim 18 wherein the reactive derivative of the acid of general formula R^5COOH is a halide, an anhydride, a mixed anhydride, an azide or an active ester.

20. A process as claimed in Claim 19 wherein the reactive derivative of the acid of general formula R^5COOH is the chloride or bromide.

21. A process as claimed in Claim 18 wherein the condensing agent is a carbodiimide.

22. A process as claimed in any one of Claims 18 to 21 wherein the compound of formula (III) as defined therein is prepared by hydrolysing a corresponding acylamino compound of general formula:



wherein R^1, R^2, R^3 and R^4 are as defined in Claim 1 and "Acyl" represents an acyl radical.

23. A process as claimed in any one of Claims 12 to 22 in which a compound of formula (I) is prepared wherein R^1 is hydrogen and that compound is lower alkylated, lower aralkylated or aroylated in the 12-position to give compounds of formula (I) wherein R^1 is lower alkyl, lower aralkyl or aroyl.

24. A process as claimed in Claim 23 wherein the compound of formula (I) wherein R^1 is hydrogen is converted to an alkali metal salt which is then reacted with a lower alkyl- or lower aralkyl halide or with an aroylating agent.

25. A process for preparing a compound as claimed in Claim 1 substantially as hereinbefore described with reference to Example 1.

26. A compound as claimed in Claim 1 whenever prepared by a process as claimed in any one of Claims 12 to 25.

27. A compound as claimed in Claim 1 substantially as hereinbefore described in any one of Examples 1 to 23.

28. A pharmaceutical composition comprising a compound of general formula (I) as defined in Claim 1 or a pharmaceutically acceptable acid addition or quaternary ammonium salt thereof, together with a pharmaceutical carrier.

29. A pharmaceutical composition as claimed in Claim 28 when in unit dosage form.

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